

Claims 18 and 19 were amended to specifically recite methods of treating a nervous system disorder, disease, or trauma in a mammal. Claims 18 and 19 also were amended to correct the misspelled word "system". Support for the amendment can be found in the specification, beginning on page 20, line 11, ending on page 21, line 12, and beginning on page 23, line 21, ending on page 24, line 2.

No new matter has been added.

Claim Objections

Claim 19 was objected because of the misspelled word "system" in step (e).

Responsive to the Examiner's objection, Claim 19 has been amended by the forgoing amendment to correct the misspelled word "system." Withdrawal of the objection is respectfully requested.

Claim Rejections under 35 U.S.C. §103

§103(a) Rejection of Claims 1-4,6,7,9,10-15 and 17-19 over Ourednik in View of Kopen

Claims 1-4, 6, 7, 9, 10-15 and 17-19 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ourednik *et al.* (Neural Stem Cells – A Versatile Tool for Cell Replacement and Gene Therapy in the Central Nervous System, *Clin. Genet.*, Vol.56, 1999) (hereinafter "Ourednik") in view of Kopen *et al.* (Marrow Stromal Cells Migrate Throughout Forebrain and Cerebellum, and They Differentiate into Astrocytes after Injection into Neonatal Mouse Brains, *PNAS*, Vol.96, 1999) (hereinafter "Kopen"). This rejection is respectfully traversed.

Neural Stem Cells are Distinct from Stem Cells of Myeloid Origin

The Examiner cites Ourednik as teaching "the utilization of neural stem cells to promote the repair of the nervous system by replacing the affected cell population by neural grafts and providing missing neuroactive molecules by expressing exogenous proteins in the transferred cells." The Examiner also states that "Ourednik further discloses that the [neural] stem cells can be stably transfected to express a desired protein, that they are able to migrate and intermingle with host cells and that they are able to differentiate and assume the phenotypes of the regions of engraftment for the treatment of neural disorders in both discrete and widespread locations." The Examiner concedes that Ourednik "fails to specifically disclose myeloid stem cells in the practice of the method." Moreover, the neural stem cells suggested by Ourednik are functionally distinct from the stem cells of myeloid origin, as disclosed in the present invention. Unlike neural stem cells, which can differentiate into neural cells, stem cells of myeloid origin, in contrast, are known for their ability to differentiate into a variety of blood and immune cells. Furthermore, Ourednik teaches that "during its maturation, the central nervous system (CNS) appears progressively to lose its restorative capacity by establishing a potent inhibitory environment to neural regrowth and the formation of new connections" (page 267), and that neural stem cells are used to repair the central nervous system due to "their potential to differentiate into various (if not all) neuronal and glial cell lineages, and to populate developing or degenerating CNS regions in multiple regional and temporal contexts" (page 269). Those skilled in the art, therefore, would not expect other (non-neural) stem cells to differentiate into neuronal and glial cells. It would not be obvious for the ordinary artisan to introduce stem cells of myeloid origin into mammalian nervous system for treatment of nervous system disorders, as claimed by the present invention.

Kopen Does Not Teach the Use of Myeloid Stems in Mouse Brains

The Examiner states that Kopen teaches that "stem cells of myeloid origin, *i.e.*, hematopoietic stem cells or marrow stromal cells, can adopt neural cell characteristics when exposed to the brain environment." The Examiner concludes that "[t]he ordinary skilled artisan would have been motivated to [use] myeloid stem cells, as disclosed in Kopen, because a supply of which is more accessible than the neural cells disclosed in Ourednik. Additionally, the ordinary skilled artisan would reasonably expect myeloid stem cells to be useful in the method disclosed by Ourednik." The Applicant respectfully traverses the rejection for the following reasons.

The three-prong test that must be met for a reference or a combination of references to be *prima facie* obvious has not been satisfied.

MPEP §2142 states:

[T]o establish a *prima facie* case of obviousness . . . there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all of the claim limitations.

These criteria have not been met.

1. Marrow Stromal Cells are Distinct from Stem Cells of Myeloid Origin

Marrow stromal cells, as disclosed by Kopen, are functionally different from hematopoietic stem cells or stem cells of myeloid origin disclosed in the present invention. Marrow stromal cells are multipotent adult stem cells that contribute to the regeneration of supporting tissues including bone, cartilage, fat and muscle. Hematopoietic stem cells or stem cells of myeloid origin, on the other hand, are known for their ability to differentiate into a variety of blood and immune cells. Moreover, Kopen discloses that after injection into developing neonatal mouse brains, marrow stromal cells mimic the behavior of neural progenitors by participating in many aspects of normal brain development,

including, among others, differentiation into astrocytes and perhaps neurons. Thus, Kopen does not suggest the introduction of stem cells of myeloid origin into neonatal mouse brains.

2. Mature CNS Poses Inhibitory Environment to Neural Regrowth.

Kopen uses marrow stromal cells in neonatal mouse brains. Early in postnatal life, the brain continues to undergo extensive development, and produces various stimuli and growth factors, etc., that are essential to the development of central nervous system. Kopen suggests that the most significant factor contributing to the behavior of marrow stromal cells is their exposure to the neonatal brain microenvironment. On the other hand, the same stimuli and growth factors that are important to the development of central nervous system are not necessarily present in the adult mouse brains. As suggested by Ourednik, "during its maturation, . . . central nervous system appears progressively to lose its restorative capacity by establishing a potent inhibitory environment to neural regrowth and the formation of new connections." Therefore, the ordinary skilled artisan would not expect marrow stromal cells, as disclosed by Kopen, to be useful in the method disclosed by Ourednik due to the potent inhibitory environment in adult mouse brains. Moreover, the ordinary skilled artisan would not expect stem cells of myeloid origin, as disclosed by the present invention, to be useful in the method disclosed by Ourednik.

In *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 923, 933 (Fed. Cir. 1984), the court states:

Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination.

Accordingly, in the absence of any teaching, suggestion or incentive, it would be improper to combine Ourednik and Kopen.

In view of the foregoing reasons, the Applicant respectfully submits that Ourednik, Kopen, or combinations thereof does not teach or suggests delivering

stem cells of myeloid origin into a nervous system, wherein the stem cells differentiate into glial and neuronal cells, as claimed by the present invention. Therefore, the rejection of Claims 1-4, 6, 7, 9, 10-15 and 17-19 under 35 U.S.C. §103(a) over Ourednik in view of Kopen is improper. Withdrawal of the rejection is respectfully requested.

§103(a) Rejection of Claims 1-7, 9, 10-15 and 17-19 over Ourednik in View of Kopen and Eglitis

Claims 1-7, 9, 10-15 and 17-19 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ourednik in view of Kopen, and further in view of Eglitis *et al.* (Hematopoietic Cells Differentiate into Both Microglia and Macrogia in the Brains of Adult Mice, *PNAS*, Vol.94, 1997) (hereinafter "Eglitis"). This rejection is respectfully traversed.

The Examiner states that Ourednik and Kopen together teach a method wherein myeloid stem cells are delivered to the nervous system of a mammal. The Examiner further cites to Eglitis as showing that "bone marrow derived cells acquire microglial antigenic markers and finds hematopoietically derived microglia in the brains of rats." The Examiner further concludes that "the ordinary skilled artisan would reasonably expect myeloid stem cells to be useful in the method disclosed by Ourednik because these cells have been shown to differentiate into neural cells, as disclosed by Kopen, and glial cells, as disclosed by Eglitis." Again, the three-prong test is not met, and the Applicant respectfully traverses the rejection for the following reasons.

Marrow Stromal Cells are Distinct from Stems of Myeloid Origin

As presented above, the ordinary skilled artisan would not expect marrow stromal cells, as disclosed by Kopen, to be useful in the method disclosed by Ourednik due to the potent inhibitory environment in adult mouse brains. Thus, the ordinary skilled artisan would not have been motivated to combine Ourednik and Kopen.

Kopen Does Not Teach Marrow Stromal Cells Differentiate into Neural Cells

Kopen teaches that after injection into developing neonatal mouse brains, marrow stromal cells mimic the behavior of neural progenitors by participating in many aspects of normal brain development, including, among others, differentiation into astrocytes and perhaps neurons. Therefore, Kopen fails to teach that marrow stromal cells are capable of differentiation into neural cells (including both astrocytes and neurons). Moreover, marrow stromal cells are functionally different from stem cells of myeloid origin. Thus, Kopen does not teach or suggest that stem cells of myeloid origin are capable of differentiation into neural cells (including both astrocytes and neurons). Therefore, the Examiner's conclusion that stem cells of myeloid origin have been shown to differentiate into neural cells, as disclosed by Kopen, is improper.

Eglitis Does Not Teach Hematopoietic Stem Cells Differentiate into Neural Cells.

Thirdly, Eglitis teaches that hematopoietic cells are capable of differentiating into glial cells after transplantation into adult mouse brains. Glial cells and neuronal cells are the two major cell types in the brain. Glial cells provide physiological support to neuronal cells. Therefore, as pointed out by the Examiner, Eglitis alone does not teach or suggest that hematopoietic stem cells are capable of differentiation into neural cells (including both glial and neuronal cells). Accordingly, those skilled in the art would not expect hematopoietic stem cells cited by Eglitis to be useful in Ourednik, which discloses use of neural progenitor cells for the repair of nervous system.

The Applicant respectfully submits that, in view of the foregoing reasons, the combination of Ourednik, Kopen and Eglitis does not teach or suggest that stem cells of myeloid origin are capable of differentiation into both glial and neuronal cells. As the case law has made clear, finding obviousness through hindsight is impermissible and refuted by the objective indicia of nonobviousness.

Therefore, in the absence of any teaching, suggestion or incentive, the rejection of Claims 1-7, 9, 10-15 and 17-19 under 35 U.S.C. §103(a) over Ourednik in view of Kopen, and further in view of Eglitis is improper. Accordingly, withdrawal of the rejection is respectfully requested.

§103(a) Rejection of Claims 1-4 and 7-19 over Ourednik in View of Kopen and Cheng

Claims 1-4 and 7-19 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ourednik in view of Kopen, and further in view of Cheng et al. (Sustained Gene Expression in Retrovirally Transduced, Engrafting Human Hematopoietic Stem Cells and Their Lympho-Myeloid Progeny, *Blood*, Vol. 92, 1998). This rejection is respectfully traversed.

The Examiner suggests that, in view of Ourednik, Kopen and Cheng, it would be obvious to one of ordinary skill in the art to use myeloid stem cells expressing the CD34 surface antigen in the present invention. Once again, the three-prong test has not been met, and the Applicant respectfully traverses the rejection for the following reasons.

Marrow Stromal Cells are Distinct from Stem Cells of Myeloid Origin

As presented above, the ordinary skilled artisan would not expect marrow stromal cells, as disclosed by Kopen, to be useful in the method disclosed by Ourednik due to the potent inhibitory environment of adult mouse brains. Thus, one of ordinary skill would not have been motivated to combine Ourednik and Kopen.

Cheng Does Not Suggest Use of CD34⁺ Cells in Nervous System

Cheng discloses that hematopoietic stem cells are included in a rare population of cells that bear the CD34 surface antigen (CD34⁺). While Cheng relates to a gene delivery system by hematopoietic stem cells into human bone marrow, Ourednik relates to the utilization of neural stem cells to promote the repair of the nervous system. Thus, there is no teaching or suggestion of using

hematopoietic stem cells expressing CD34 to promote the repair of the central nervous system, as disclosed by Ourednik.

Moreover, Kopen relates to the introduction of marrow stromal cells into neonatal mouse brains. As presented above, marrow stromal cells are functionally different from hematopoietic stem cells. Thus, those skilled in the art would not expect hematopoietic stem cells expressing CD34 to be useful in the method disclosed by Kopen.

In view of the foregoing reasons, the Applicant respectfully submits that there is no suggestion, teaching or incentive in the prior art to combine Ourednik, Kopen and Chung. Therefore, the rejection of Claims 1-4 and 7-19 under 35 U.S.C. §103(a) over Ourednik in view of Kopen, and further in view of Cheng is improper. Withdrawal of the rejection is respectfully requested.

Claim Rejections under 35 U.S.C. §112 First Paragraph

Claims 1-19 are rejected by the Examiner under 35 U.S.C. §112, first paragraph, as the specification, while being enabling for methods drawn to mouse and rat models, does not reasonably provide enablement for methods drawn to the treatment of human subjects. This rejection is respectfully traversed.

Human Clinical Trials are not required

MPEP §2107.02 states:

There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders.

MPEP §2164.03 further states:

An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention . . . A rigorous or an invariable exact correlation is not required.

The specification provides as examples two animal models, rat and mouse, wherein the stem cells isolated from a human donor were administered into the nervous system of Parkinsonian rats and mice. It is well known to those skilled in the art that rats and mice are the most commonly used mammal in clinical research and that experimental success in lab animals generally correlates with similar efficacy in higher mammals. Thus, the examples utilizing Parkinsonian rats and mice are sufficient to indicate the efficacy of the method in other mammals, including human.

In addition, the Applicant respectfully submits herewith the U.S. Patent 5,928,947 to Anderson *et al.*, claiming a method of delivering genetically engineered mammalian neural stem cells into an animal with a nervous system disorder. The only evidence supporting the Anderson *et al.* claims was *in vitro* data of rat neural stem cells. Thus, the *in vitro* model utilized by Anderson *et al.* is not nearly as physiologically relevant to the human nervous system as are the Parkinsonian mouse and rat models of the present specification. Therefore, the Applicant respectfully submits that the mouse and rat models, used in the present invention, should be accepted as valid evidence establishing efficacy of myeloid stem cell treatment of nervous system disorders in other mammals, including human.

Robinson
Property not
precedent
of Anderson et al.
5,928,947
app. not
relevant to
present app.

Stem Cells of Myeloid Origin are Effective Gene Delivery Vehicles

The Examiner cites Martinez, as teaching that the research on neural stem cells and progenitors in the developing and adult CNS "is still in its infancy, and our knowledge of the biological mechanisms regulating maturation and differentiation of multipotent neural progenitors remains highly incomplete." The Applicant respectfully submits that a rejection based on the incomplete understanding of the biological mechanism behind the regulation of stem cell maturation and differentiation is improper. As the court states in *In re Cortright*, 49 USPQ 2d 1464, 1469 (Fed. Cir. 1999):

It is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works . . .

Furthermore, statements that a physiological phenomenon was observed are not inherently suspect simply because the underlying basis for the observation cannot be predicted or explained.

The Examiner further cites Martinez as expressing that "further improvement in gene transfer procedures is needed," and that it also is necessary to "explore efficient regulatable expression system and safety mechanisms which will make it possible to modulate or switch off the production of a transferred protein, or even eliminate the cells themselves if necessary." The Applicant respectfully disagrees. Martinez was published in 1997. Since then, and prior to the instant invention, great progress has been made in gene therapy research. A variety of suitable viral vectors and regulatable expression systems have been developed, such as, AVV-derived, and SV40-derived gene delivery systems. In addition, a number of clinical trials have been done using stem cells as gene delivery systems. Both effectiveness and safety are demonstrated by these trials. Moreover, it is well known to those skilled in the art, and also acknowledged by the Examiner on page 6 of the Office Action, "myeloid stem cells, cells derived from hematopoietic cells, make attractive targets and vehicles for somatic cell-based gene therapy because they have the ability to continue producing the therapeutic gene indefinitely." Furthermore, the need for improvement, as stated by Martinez in 1997, should not render the present invention ineffective.

*Still have
find out*

In view of the forgoing reasons, the Applicant respectfully submits that, to those skilled in the art, the specification of the present Application is enabled for methods of delivering stem cells of myeloid origin in mammals, including human, for treating neurological disease in mammals, including human subjects.

Claim Rejections under 35 U.S.C. §112 Second Paragraph

§112 Second Paragraph Objection of Claims 1-19

Withdraw
Claims 1-19 are rejected by the Examiner under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Responsive to the Examiner's rejection of Claims 1-19, Claims 1, 2, 10, 11, 18 and 19 have been amended (*supra*).

Claim 1 was amended to specifically recite the method of targeted delivery of mammalian stem cells.

Claims 2 and 11 were amended by changing the word "derived" to "isolated." The Applicant respectfully submits that amended Claims 2 and 11 are definite.

Claim 10 was amended to specifically recite a method of treating disorders, diseases, or trauma of a nervous system of a mammal, and to correct the misspelled word "system."

Claims 18 and 19 were amended to specifically recite methods of treating a nervous system disorder, disease, or trauma in a mammal, and to correct the misspelled word "system."

By the foregoing amendment, the Applicant respectfully submits that Claims 1-19 are definite and specifically claim the subject matter. Withdrawal of the rejection is respectfully requested.

Therapeutic Amount, as Disclosed in the Present Invention, is Definite

The Examiner further states that "[the] instant claims recite the limitation that the claimed method comprises administering a "therapeutic amount" of mammalian stem cells of myeloid origin," and "without clarification, the term, "therapeutic amount," remains unclear". The Applicant respectfully disagrees.

MPEP §2164.01(c) states:

[I]t is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation.

In addition, as stated by the CCPA in *In re Naquin*, 398 F.2d 863, 158 USPQ 317, 319 (C.C.P.A. 1968):

The specification need describe the invention only in such detail as to enable a person skilled in the most relevant art to make and use it. When an invention, in its different aspects, involves distinct arts, that specification is adequate which enables the adepts of each art, those who have the best chance of being enabled, to carry out the aspect proper to their specialty.

On page 18, lines 1-3, the present Application specifies, in one embodiment, that neonatal rats and mice pups aged 24-36 hrs were injected intracerebroventricularly with 2,000 to 8,000 stem cells. Further on page 18, lines 5-9, the present Application specifies, in another embodiment, that rats weighing between 320g and 400g were injected intracerebroventricularly with 8,000 stem cells. Also, on pages 22-23, lines 29-9, the specification states that the assessment of the clinical features and the design of an appropriate *therapeutic regimen* for the individual patient is ultimately the responsibility of the prescribing physician. The specification further provides guidance to the prescribing physician that the magnitude of an administered dose in the management of the disorder of interest should be based on the severity of the condition to be treated, the patient's individual physiology, biochemistry etc., and the route of administration. The specification further teaches that the prescribing physician should consider each patient's age, body weight, sex and response when determining the dose and dose frequency. The Applicant respectfully submits that the present Application has disclosed sufficient direction and guidance in such a way that those skilled artisans, *i.e.*, prescribing physicians, may use to determine the "therapeutic amount" for each individual subject without undue experimentation. Thus the term "therapeutic amount" as recited by the instant claims is clear.

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In light of the foregoing remarks, the Applicant respectfully requests reconsideration of Claims 1-19. Prompt reconsideration and allowance of Claims 1-19 are earnestly solicited.

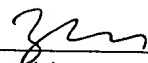
Respectfully submitted,

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02/28/02

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VERSION WITH MARKING TO SHOW CHANGES MADE

In the Claims:

1. (Amended) A method of targeted delivery of mammalian stem cells of myeloid origin into a nervous system of a mammal, ~~comprising~~ by

(a)—administering a therapeutically effective amount of mammalian stem cells of myeloid origin into ~~a~~ said nervous system of said mammal; whereby

(b)—~~migrating of~~ said mammalian stem cells of myeloid origin migrate from the ~~an~~ injection site to a preferred site in ~~a~~ said nervous system of said mammal; and

(c)—~~engrafting of~~ said mammalian stem cells of myeloid origin engraft into said nervous system of said mammal at said preferred site.

2. (Amended) The method of **Claim 1**, wherein said mammalian stem cells of myeloid origin are ~~derived~~ isolated from at least one of the group of bone marrow, mobilized peripheral blood, umbilical cord blood, or fetal liver tissue from a mammal.

10. (Amended) A method of treating disorders, diseases, or trauma of a nervous system of a mammal, ~~comprising~~ by

(a)—administering a therapeutically effective amount of mammalian stem cells of myeloid origin into ~~a~~ said nervous system of said mammal; whereby

(b)—~~migrating of~~ said mammalian stem cells of myeloid origin migrate from the ~~an~~ injection site to a preferred site in ~~a~~ said nervous system of said mammal; and

(c)—~~engrafting of~~ said mammalian stem cells of myeloid origin engraft into said nervous system of said mammal at said preferred site; and

~~(d) — differentiating of said engrafted mammalian stem cells of myeloid origin of step (c)~~differentiate into neuronal and glial cells; ~~and~~
~~(e) — replacing damaged nervous system tissue of said mammal with said neuronal and glial cells of step (d)~~replace damaged nervous system tissue.

11. (Amended) The method of **Claim 10**, wherein said mammalian stem cells of myeloid origin are ~~derived~~isolated from at least one of the group of bone marrow, mobilized peripheral blood, umbilical cord blood, or fetal liver tissue from a mammal.

18. (Amended) A method of treating ~~a nervous system disorders, diseases, or trauma of a nervous system in of~~ a mammal, ~~comprising by~~

~~(a) — administering a therapeutically effective amount of mammalian stem cells of myeloid origin into a said nervous system of said mammal, wherein said mammalian stem cells are transiently or stably genetically engineered by at least one viral vector or by non-viral transfection; whereby~~

~~(b) — migrating said mammalian stem cells of myeloid origin migrate from the an injection site to a preferred site in a said nervous system of said mammal;~~

~~(c) — engrafting said mammalian stem cells of myeloid origin engraft into said nervous system of said mammal at said preferred site;~~

~~(d) — differentiating said engrafted mammalian stem cells of myeloid origin of step (c)~~differentiate into neuronal and glial cells; ~~and~~

~~(e) — replacing damaged nervous system tissue of said mammal with said neuronal and glial cells of step (d)~~replace damaged nervous system tissue.

19. (Amended) A method of treating ~~a nervous system disorders, diseases, or trauma of a nervous system of in~~ a mammal, ~~comprising by~~

(a)—administering a therapeutically effective amount of mammalian stem cells of myeloid origin into a said nervous system of said mammal, wherein said stem cells of myeloid origin deliver viral vectors, other transducing agents, or biological pumps of peptides directly into said nervous system of said mammal; whereby

(b)—~~migrating~~ said mammalian stem cells of myeloid origin migrate from the ~~an~~ injection site to a preferred site in a said nervous system of said mammal;

(c)—~~engrafting~~ said mammalian stem cells of myeloid origin engraft into said nervous system of said mammal at said preferred site;

(d)—~~differentiating~~ said engrafted mammalian stem cells of myeloid origin ~~of step (c)~~ differentiate into neuronal and glial cells; and

(e)—~~replacing damaged nervous system tissue of said mammal with said neuronal and glial cells of step (d)~~ replace damaged nervous system tissue.